STIs... *the resurgence of old foes*

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- The HIV/STD/TB/Hepatitis Program and the Dakotas AIDS Education and Training Center (DAETC) conduct monthly Lunch and Learn Webinars for health care professionals in North and South Dakota.

- Each month a new topic will be held from 12:00 p.m. to 1:00 p.m. CST on the fourth Wednesday of the month.

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Disclosures

No conflicts of interest or relationships to disclose

Urethral itching

- 48 y/o married man calls in c/o urethral itching x 3 days
- No urethral discharge, no burning with urination; no unusual odors
- Wife is not having symptoms
- PMH significant for ADD, GERD & OA
- Differential diagnosis? Diagnostic plan?

Urethral itching (cont.)

My hypothesis:

- The urethral itching is likely either caused by a sexually-transmitted urethritis (e.g. Chlamydia) or early balanitis (typically caused by Candida).

Plan:

- UA with micro
- urine GC/CT PCR
    - Pathogen-directed antibiotics if organism detected
    - If nothing on PCR/urine culture, prescribe:
        * fluconazole 200mg PO x 1 for balanitis.

Balanitis

- defined as inflammation of the glans penis
- symptoms generally evolve over 3 to 7 days
- often presents as pain, tenderness, &/or pruritus of the glans and/or foreskin
- Physical examination shows erythema +/- a curd-like or purulent exudate +/- ulcerations (depending on the etiology)
- Candida albicans is the most common etiology
- Less common etiologies: *Gardnerella vaginalis* (foul-smelling discharge), Group A streptococcus, *Staph aureus*, *Trichomonas vaginalis*, HSV, HPV, syphilis, scabies, and *Mycoplasma genitalium*

Urethral itching (cont.): Results

- UA with 5 WBCs/trace leukoesterase
  - Rare WBC clumps and urine mucous
  - Urine culture negative
- Urine Chlamydia trachomatis PCR: **detected**
- Urine Neisseria gonorrhea PCR: not detected
- Doxycycline 100mg PO bid x 7 days prescribed
  - Urethral itching resolved

CHLAMYDIA
CDC Treatment Guidelines

Recommended Regimens

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Levofloxacin 500 mg orally once daily for 7 days

OR

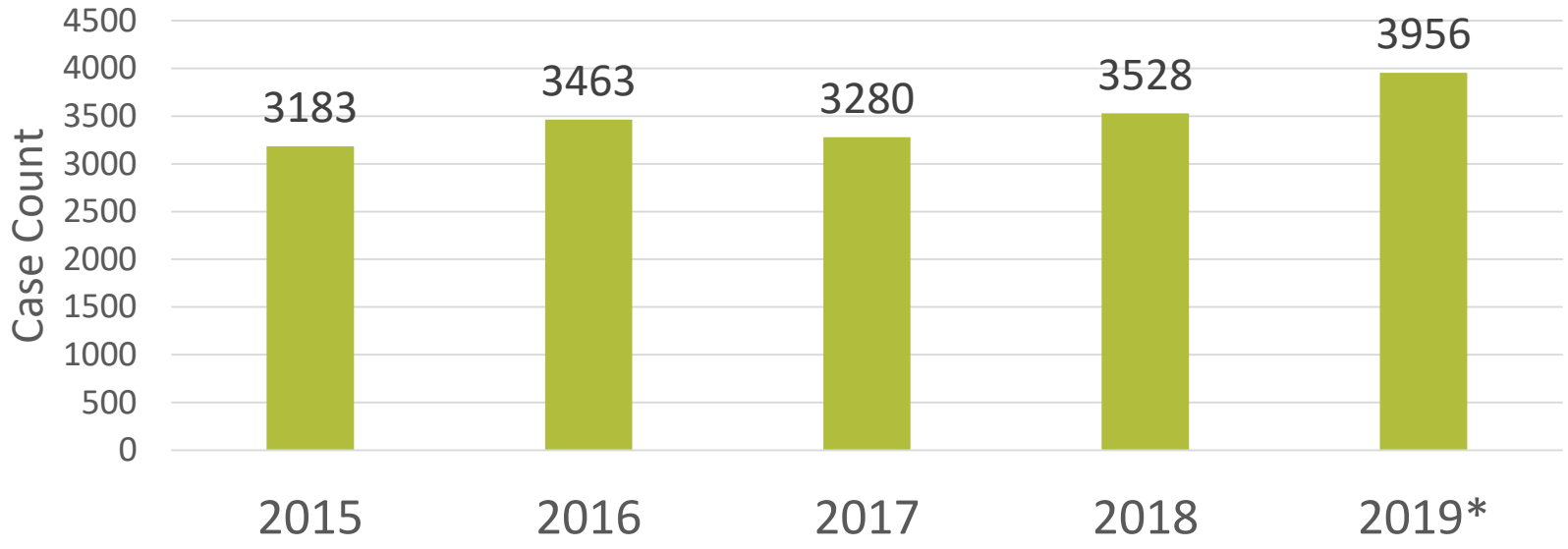
Ofloxacin 300 mg orally twice a day for 7 days

http://www.cdc.gov/std/tg2015/chlamydia.htm

Urethral itching (cont.): Results

- Patient and his wife are “swingers”
- Wife subsequently underwent STI screening, which was positive for gonorrhea and Chlamydia in the pharynx
- His last sexual exposure aside from his wife was ~3 weeks prior to his diagnosis
- Underscores the importance of routine STI screening in asymptomatic individuals who are at risk for STIs based on sexual practices

Chlamydia, North Dakota 2015-2019*



Source: NDDoH Division of Disease Control

*Prelimina

Urethritis

- Consider a diagnosis of urethritis if
  - The patient c/o urethral discharge
  - The patient c/o burning/itching at the urethral meatus
  - The patient c/o dysuria
    - the UA with micro has 10+ WBCs/HPF or urine dip (+) for LE; urine culture is typically negative
- Obtain GC/CT PCR of the urine to confirm the diagnosis (Gonorrhea/Chlamydia NAAT)
    - ≥2 white blood cells (WBCs) per oil immersion field from the Gram stain of a urethral swab is suggestive

Etiology of Urethritis

Gonococcal Urethritis

- ***Neisseria gonorrhea***

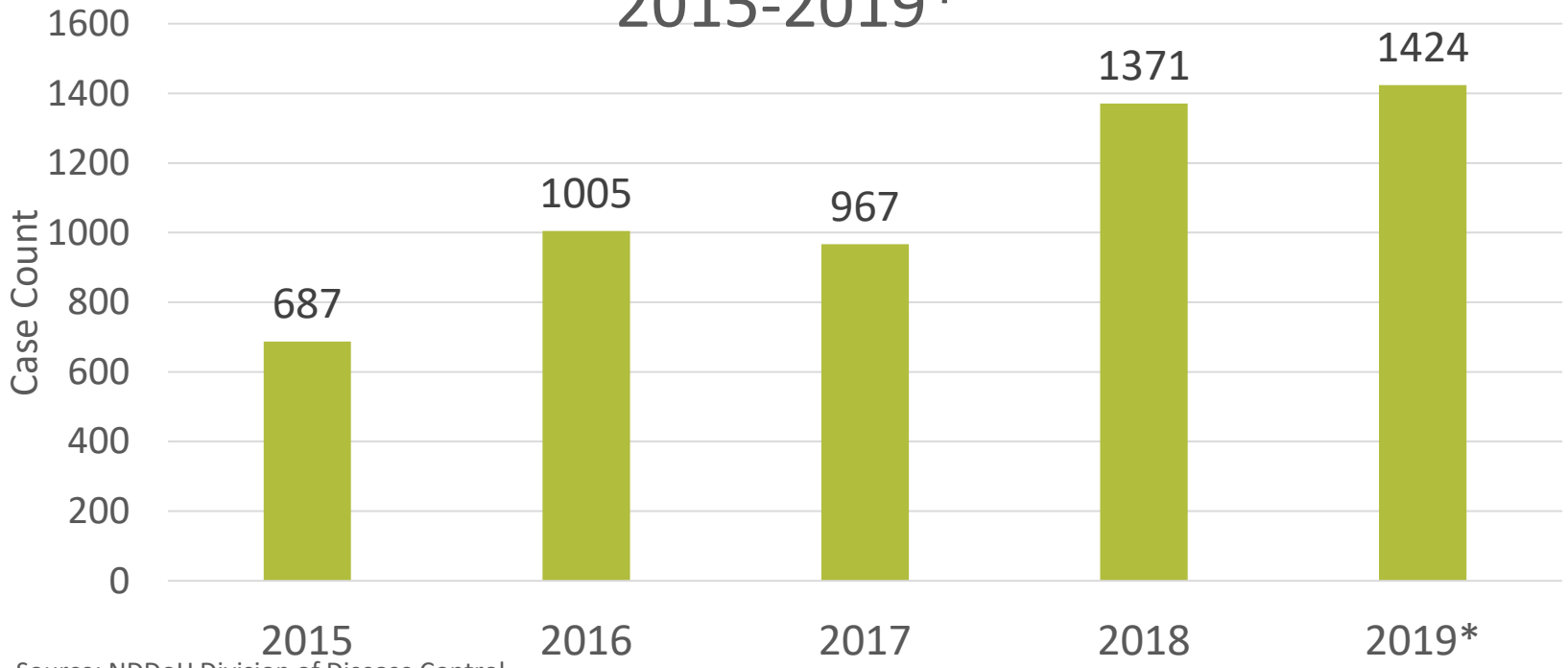
Non-Gonococcal Urethritis (NGU)

- *Chlamydia trachomatis* (15-40%)
- *Ureaplasma urealyticum*
- *Mycoplasma genitalium* (15-25%)
- *Trichomonas vaginalis*
- Herpes simplex virus

  (usually accompanied by painful ulcers or vesicles)

Slide Courtesy Hillary Liss, MD University of Washington

Gonorrhea, North Dakota 2015-2019*



Source: NDDoH Division of Disease Control

*Preliminary

2015 Updated Gonorrhea Treatment Guidelines

Uncomplicated Gonococcal Infection of Pharynx, Cervix, Urethra, or Rectum

RECOMMENDED THERAPY

Ceftriaxone
250 mg IM x 1

+

Azithromycin
1 g PO x 1

NOTES:

- Dose of ceftriaxone now 250 mg (previously 125 mg)
- Doxycycline changed to alternative due to high rate of tetracycline resistance (23.7% in 2013)
- Cefixime NOT first line anymore
- Fluoroquinolones NOT recommended

Source: CDC and Prevention. MMWR. 2015.64(3). http://www.cdc.gov/std/tg2015/gonorrhea.htm
Slide Courtesy Hillary Liss, MD University of Washington

2015 Updated Gonorrhea Treatment Guidelines

Uncomplicated Gonococcal Infection of Cervix, Urethra, or Rectum
Alternative Therapy (Only if Ceftriaxone not an option)

Cefixime
400 mg PO x 1

+

Azithromycin
1 g PO x 1

NOTES:

- Alternative regimens for use only when ceftriaxone not available
- Doxycycline changed to alternative due to high rate of tetracycline resistance (23.7% in 2013)
- NOT RECOMMENDED FOR USE IN PHARYNGEAL INFECTION
- If treatment failure, need culture and sensitivity, notify Public Health

Source: CDC and Prevention. MMWR. 2015.64(3). http://www.cdc.gov/std/tg2015/gonorrhea.htm
Slide Courtesy Hillary Liss, MD University of Washington

2015 Updated Gonorrhea Treatment Guidelines

PENICILLIN ALLERGY
RECOMMENDED THERAPY

Gentamicin
240 mg IM x 1

OR

Gemifloxacin
320 mg PO x 1

+

Azithromycin
2 g PO x 1

NOTES:
- Urogenital infections only
- Nausea is a common side effect of these regimens

Source: CDC and Prevention. MMWR. 2015.64(3). http://www.cdc.gov/std/tg2015/gonorrhea.htm
Slide Courtesy Hillary Liss, MD University of Washington

Any downside to the new regimens?

Nausea was common

- 27% for gentamicin + azithro
- 37% for gemifloxacin + azithro

3% and 7% in each group vomited <1 hr after administration

Slide Courtesy Hillary Liss, MD University of Washington

Etiology of Urethritis

Gonococcal Urethritis

- *Neisseria gonorrhoea*

Non-Gonococcal Urethritis (NGU)

- ***Chlamydia trachomatis (15-40%)***
- *Ureaplasma urealyticum*
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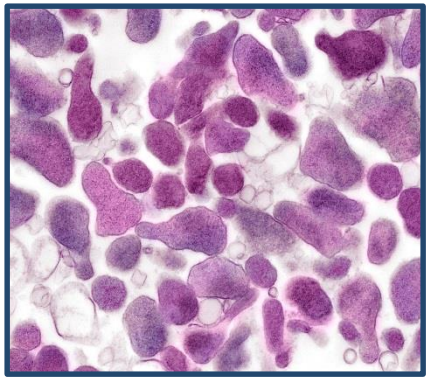
- *Trichomonas vaginalis*
- Herpes simplex virus

  (usually accompanied by painful ulcers or vesicles)

Slide Courtesy Hillary Liss, MD University of Washington

Mycoplasma genitalium

- Recognized cause of urethritis
- Role in cervicitis and PID emerging
- FDA approved *M. genitalium* NAAT in 2019
  - NAAT 90% sensitive for female vaginal & male urine specimens in a study with 11,774 specimens
- Suspect in persistent or recurrent urethritis and consider in persistent cervicitis and PID
- Treatment implications
  - Azithromycin better than doxycycline, but…
    - Emerging resistance to azithromycin
  - Moxifloxacin for failure to respond/recurrence
    - 400mg PO QD x 7 days



Initial Slide Courtesy Hillary Liss, MD University of Washington, with f/u edits

Case 2: Anal pain

- 53 y/o white male with HIV c/o anal pain
  - Preceded by “boils” around the anus
- Pt had been off of antiretroviral therapy for 2-3 years because of adherence issues
- HIV RNA PCR = 348,505 copies/ml
- CD4 count = 319
- PMH notable for HTN
  - Prior complications of HIV: thrush & seborrheic dermatitis
- Pt drinks a significant amount of EtOH and smokes heavily

Case 2: Anal pain (cont.)

- On exam,
  - circumferential region surrounding anus very erythematous with some ulceration/ breakdown
  - multiple half cm scabbed over, raised lesions
  - no frank vesicles or bullae visible
  - thin, white discharge from anus
  - significant tenderness upon insertion of swab for microbiology collection

Proctitis

- Consider a diagnosis of proctitis in a patient who c/o anorectal discharge and/or pain (esp. if MSM)
- Obtain serum RPR/syphilis EIA screening
- Obtain viral swab for HSV DNA PCR (if painful)
- Obtain Aptima swab of rectum for GC/CT PCR

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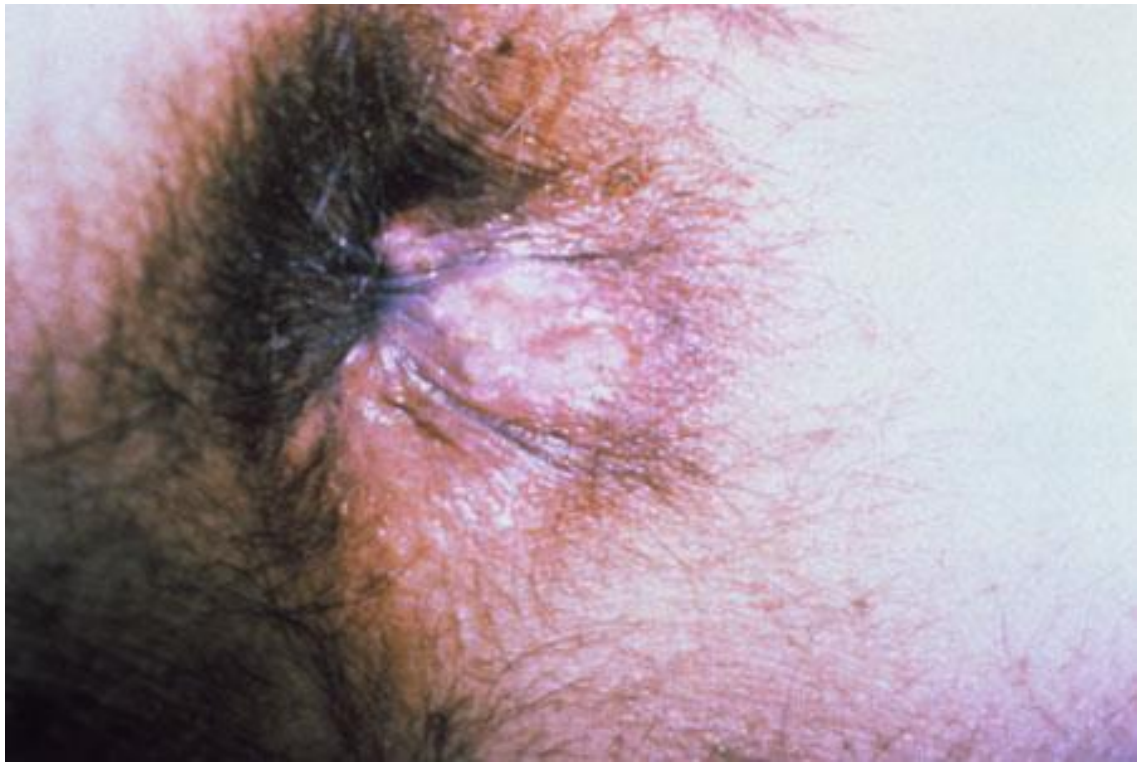
Peri-anal HSV



Slide courtesy of Dr. Paul Volberding, UCSF/San Francisco VA

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Case 2: Anal pain (cont.)

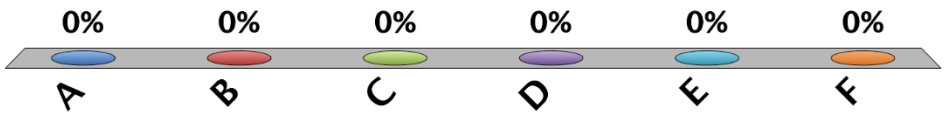
- Patient was started on acyclovir 400mg PO bid x 10 days
- Pain resolved and all signs of anal skin erosion and inflammation resolved
- Patient was then started on prophylactic acyclovir 400mg PO bid with the plan to continue until he had sustained virologic suppression after re-initiation of antiretroviral therapy

CASE 3

A 27 year old previously healthy man presents to an urgent care center with fever, sore throat, lymphadenopathy, severe fatigue and a diffuse erythematous rash. His symptoms have been present for approximately 48 hours and his history reveals unprotected receptive anal intercourse with another man 12 days prior to the onset of his symptoms. He had a negative HIV antibody test approximately 6 months ago. His physical examination shows a temperature of 39.0 C, lack of exudative pharyngitis, the presence of cervical and axillary lymphadenopathy, and a generalized morbilliform rash. All laboratory tests are pending.

Which of the following is the most likely diagnosis?

A. Syphilis
B. Acute HIV Infection
C. Shingles
D. Measles
E. Drug Hypersensitivity
F. None of the Above



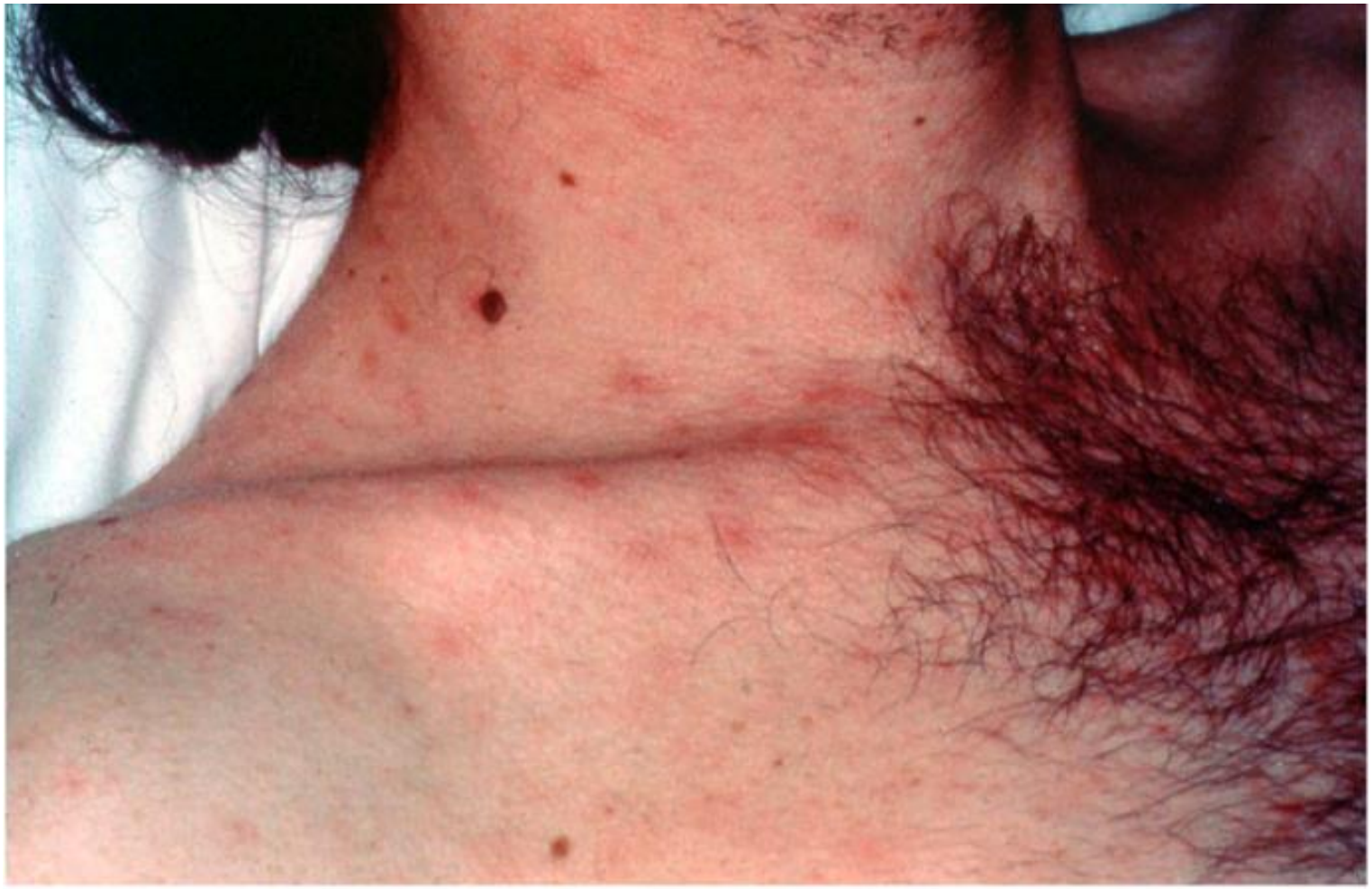


Figure 1 – Morbilliform Rash

This patient presented with a macular rash most prominent on the neck, chest, back, and abdominal region. The numerous lesions were flat, erythematous, and non-blanching.

HIVWebStudy.org

Primary HIV Infection

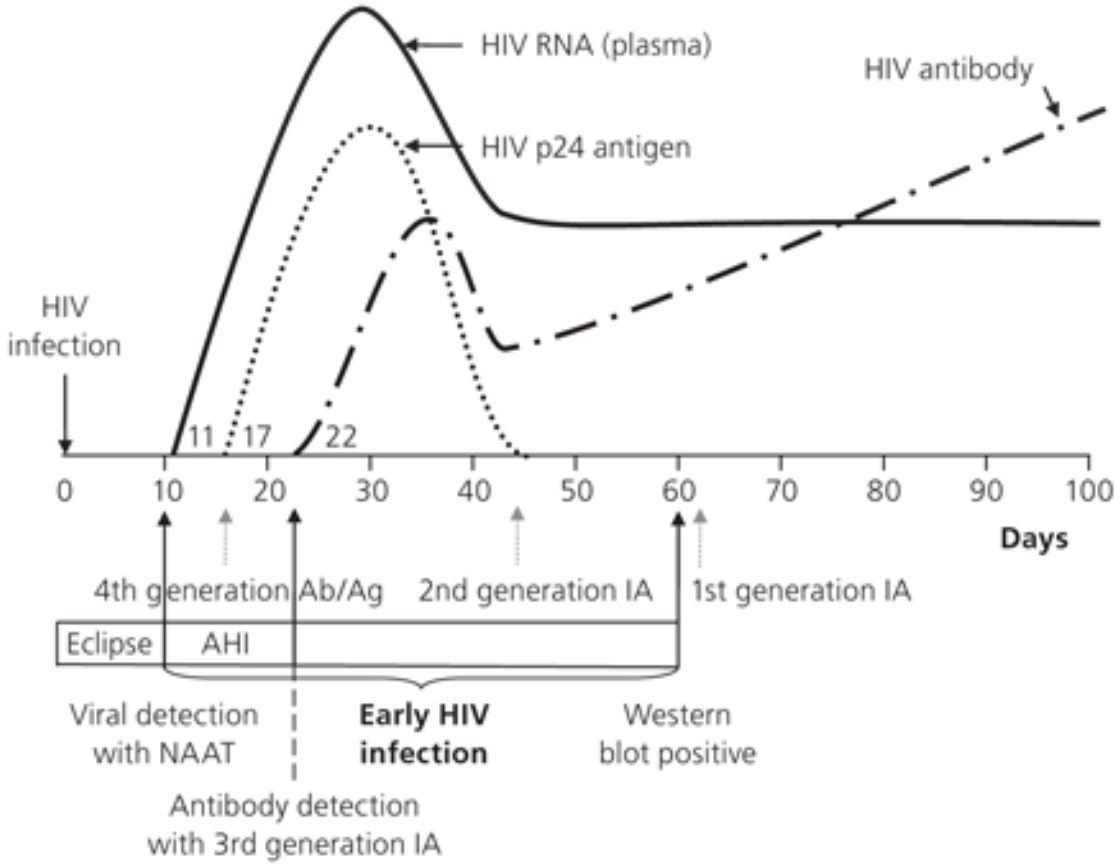
- symptomatic in many newly infected individuals
- symptoms occur 2-6 weeks after exposure to HIV
- median duration of symptoms 15-28 days

TABLE 5. Expected frequency of associated signs and symptoms among persons with signs and symptoms of acute retroviral syndrome

Symptom/sign	%
Fever	96
Lymphadenopathy	74
Pharyngitis	70
Rash Erythematous maculopapular with lesions on face, trunk and sometimes extremities, including palms and soles; mucocutaneous ulceration involving mouth, esophagus or genitals	70
Myalgia or arthralgia	54
Diarrhea	32
Headache	32
Nausea and vomiting	27
Hepatosplenomegaly	14
Weight loss	13
Thrush	12
Neurologic symptoms Meningoencephalitis or aseptic meningitis; peripheral neuropathy or radiculopathy; facial palsy; Guillain-Barré syndrome; brachial neuritis; or cognitive impairment or psychosis	12

MMWR Recommendations and Reports, January 21, 2005 / 54(02);1-20

HIV Tests: Time to Positivity



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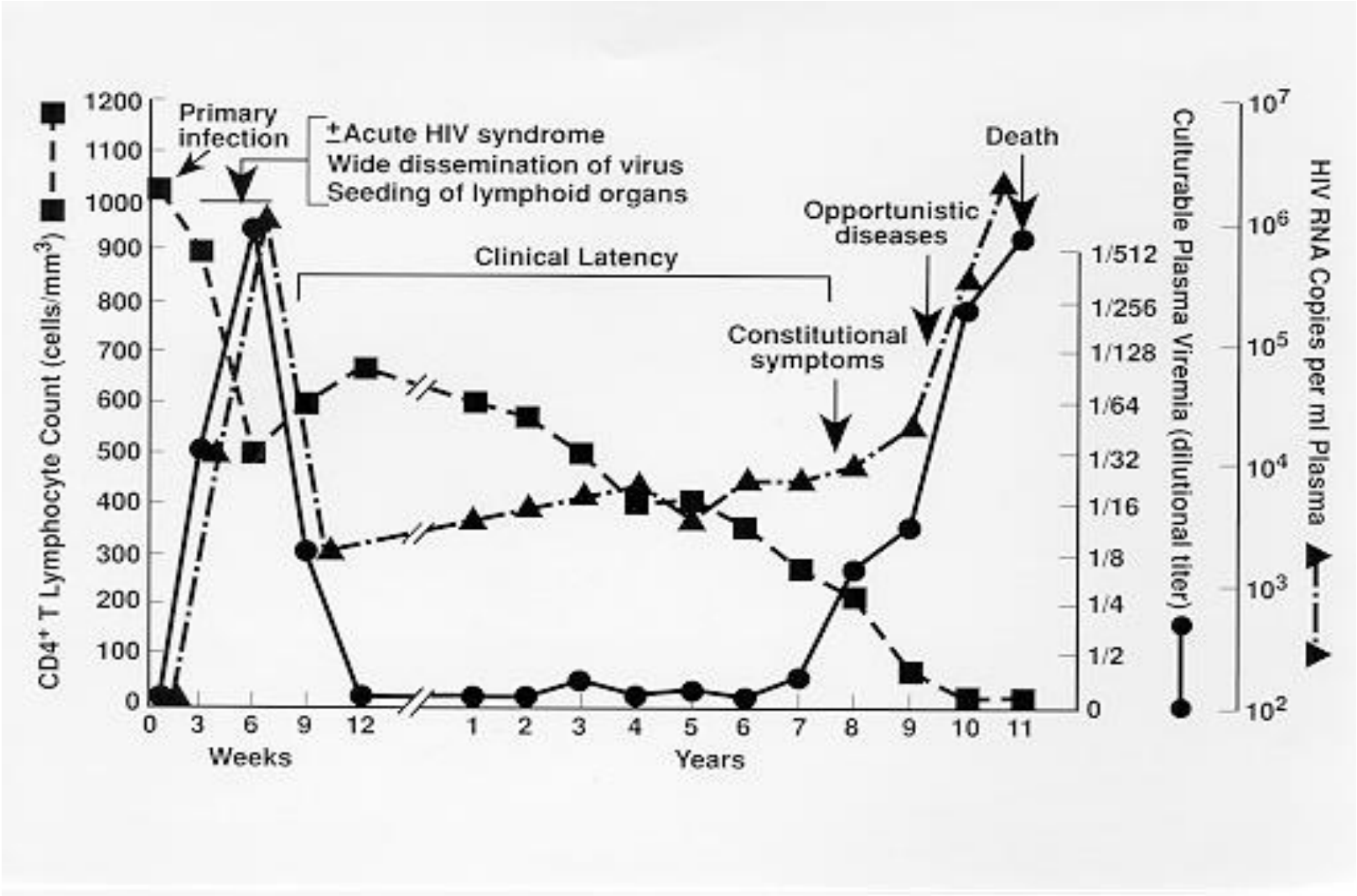
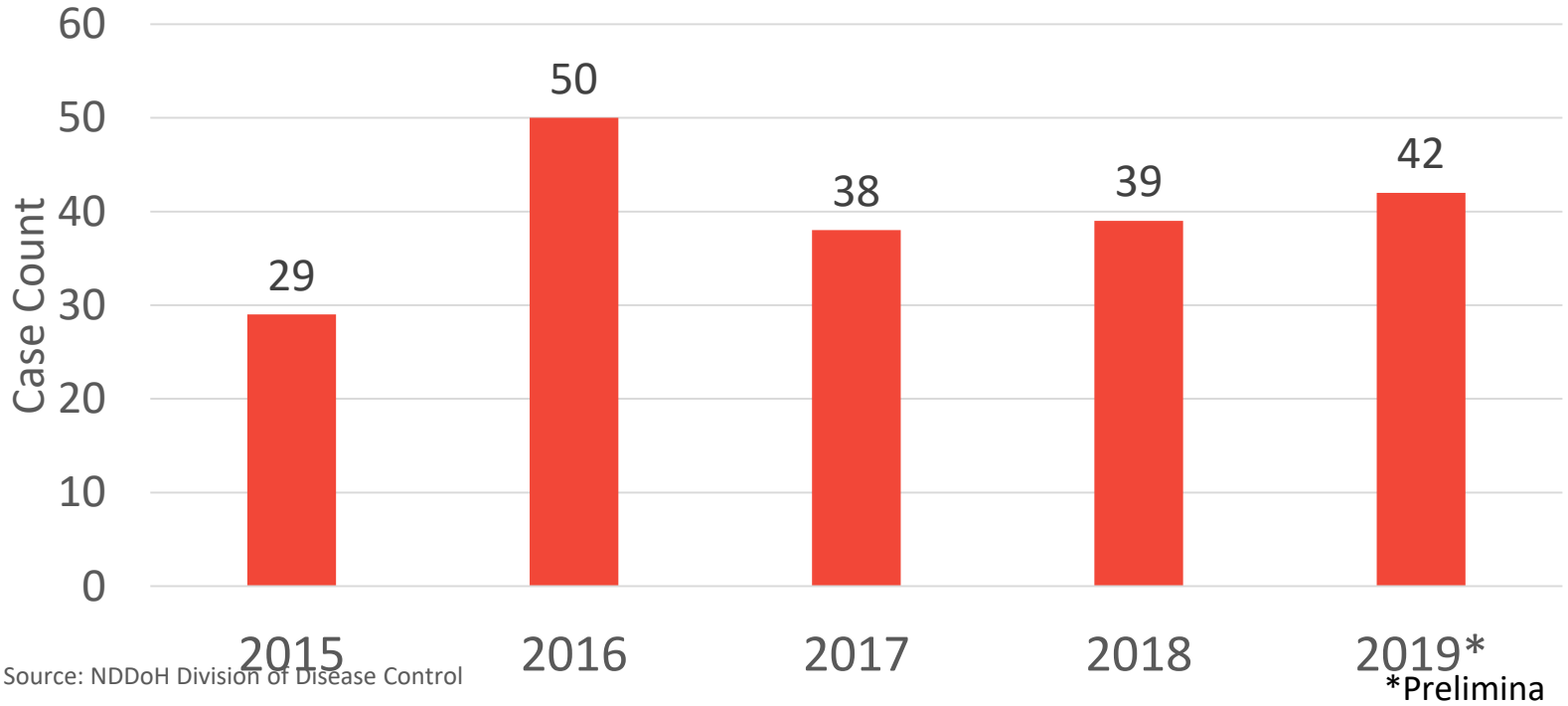
Natural History of Untreated HIV Infection



HIV/AIDS Incidence, North Dakota 2015-2019*



Source: NDDoH Division of Disease Control

*Prelimina

Case 4: 57 y/o white male with HIV

- presented to clinic in January 2013 with:
  - L shoulder pain x 10-14 days
  - nightsweats
  - sore throat
  - lymph node swelling in neck
  - chest soreness
  - knee soreness → difficulty walking
- CD4 count 8 weeks prior was 611/24%
- Undetectable HIV viral load since October 2000

PMH and Social History

- HIV/AIDS
  - CD4 nadir = 7 in 2000
  - h/o PCP pneumonia, CMV cholangitis, Candidal esophagitis, wasting syndrome
  - Antiretrovirals: AZT/3TC/ABC + nevirapine
- Hepatitis C
  - Genotype 1; awaiting treatment
  - Liver biopsy 2008: Grade 1-2, Stage 1-2
- Chronic low back pain/sciatica

- smokes 1 cigar daily and drinks 2 beers per week
- works as a bouncer at a club in NW Portland
- monogamous with male sexual partner; reports always uses condoms with intercourse

Physical Exam

Vitals:

T: 97.7 F (36.5 C)
P: 93
R: 18
B/P: 119/76
Wt: 166.60 lb (75.73 kg); Body Mass Index: 23

Exam:

Gen: A, A, O x 3, looks tired, pale and uncomfortable, difficulty getting up out of waiting room chair
ENT: mild pharyngeal erythema, no exudate, no thrush, no lesions
Neck: supple, tender, pea-sized, bilateral anterior cervical LAD
Heart: RRR, no M appreciated
Lungs: bilat CTA
Shoulders: no erythema, no edema/effusion, no calor, mild tenderness to palpation; decreased active ROM to 90 degrees (normally 180 degrees); passive ROM better (e.g. I helped him put his coat on, raising his arms above 90 degrees)
Neuro: CN 2-12 intact; sensation to light touch intact; UE MS 5/5 distally, but only 4/5 @ bilat deltoids; LE MS: R proximal 4/5, L proximal 3/5, R distal 5/5, L distal 4/5
Skin: flaky & oily rash on head most pronounced in eyebrows & nasolabial folds c/w seborrheic dermatitis

Differential??

What labs do you want to order?

Differential

- post-influenza myositis/myasthenia
- mononeuritis multiplex
- acute brachial plexus neuritis
- paraneoplastic process
- polymyalgia rheumatica – PMR
- dermatomyositis

Lab Results

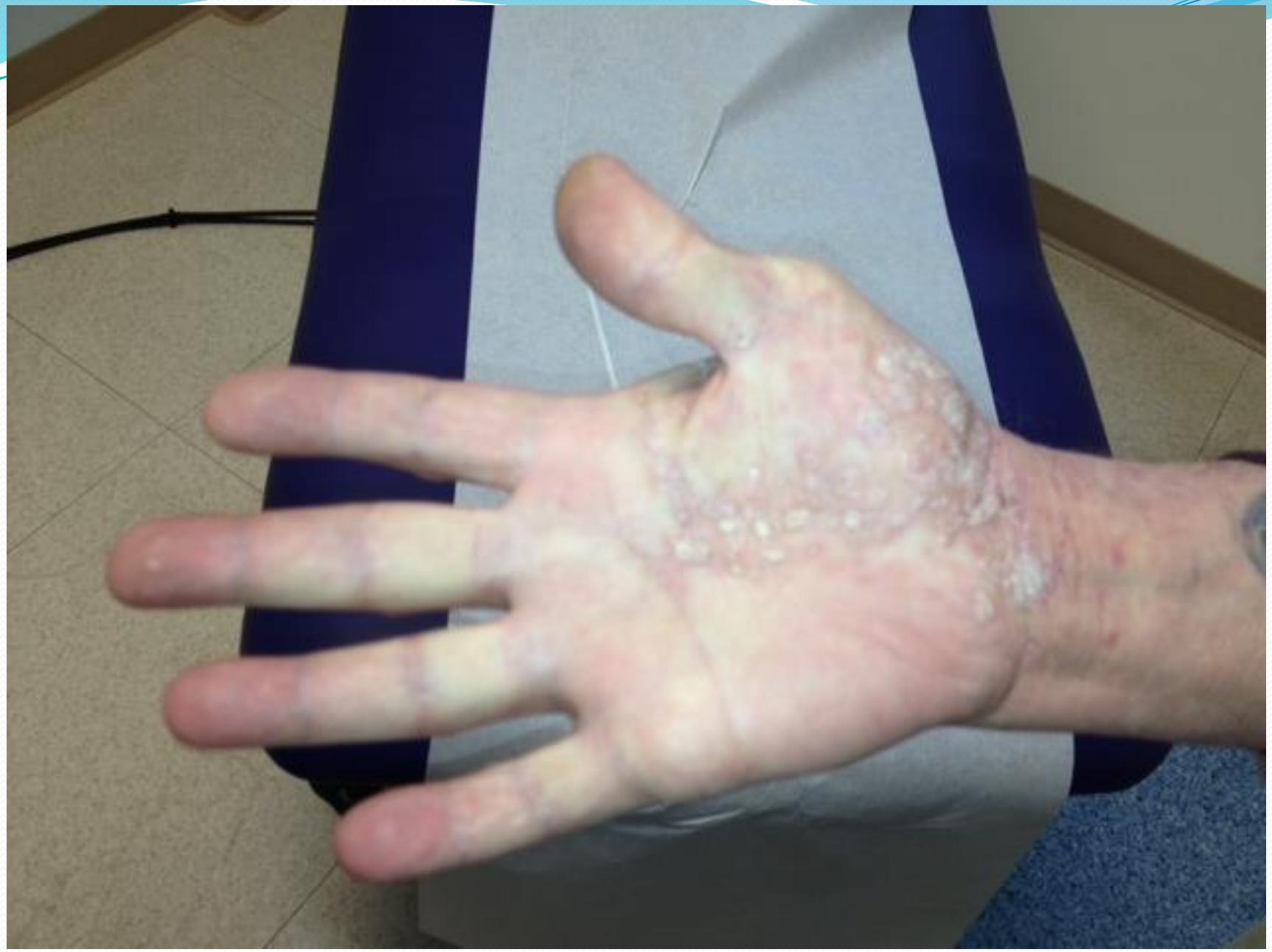
- WBC 8.5, HCT 39, platelets 305
- Chem 7 normal
- SGOT 32, SGPT 42, alk phos 199, bili 0.5
- CPK 44
- HIV RNA PCR undetectable
- CD4 count 467/25%
- ESR 80, CRP 13.4
- Quantiferon negative
- RPR non-reactive

Progression

- Worsening of pain – bilateral shoulders, bilateral knees, bilateral ankles, and both thumbs, but no e/o inflammation at any of these joints
- Rheumatology consult for migratory polyarthralgias + markedly elevated ESR/CRP. ? Giant cell arteritis

At f/u 4 weeks later…

- Patient feeling better
- shoulder pain almost resolved
- new hair loss on scalp & face
- new lichenified small plaques in the center of the palms of both hands with a few faint circular macules around the periphery

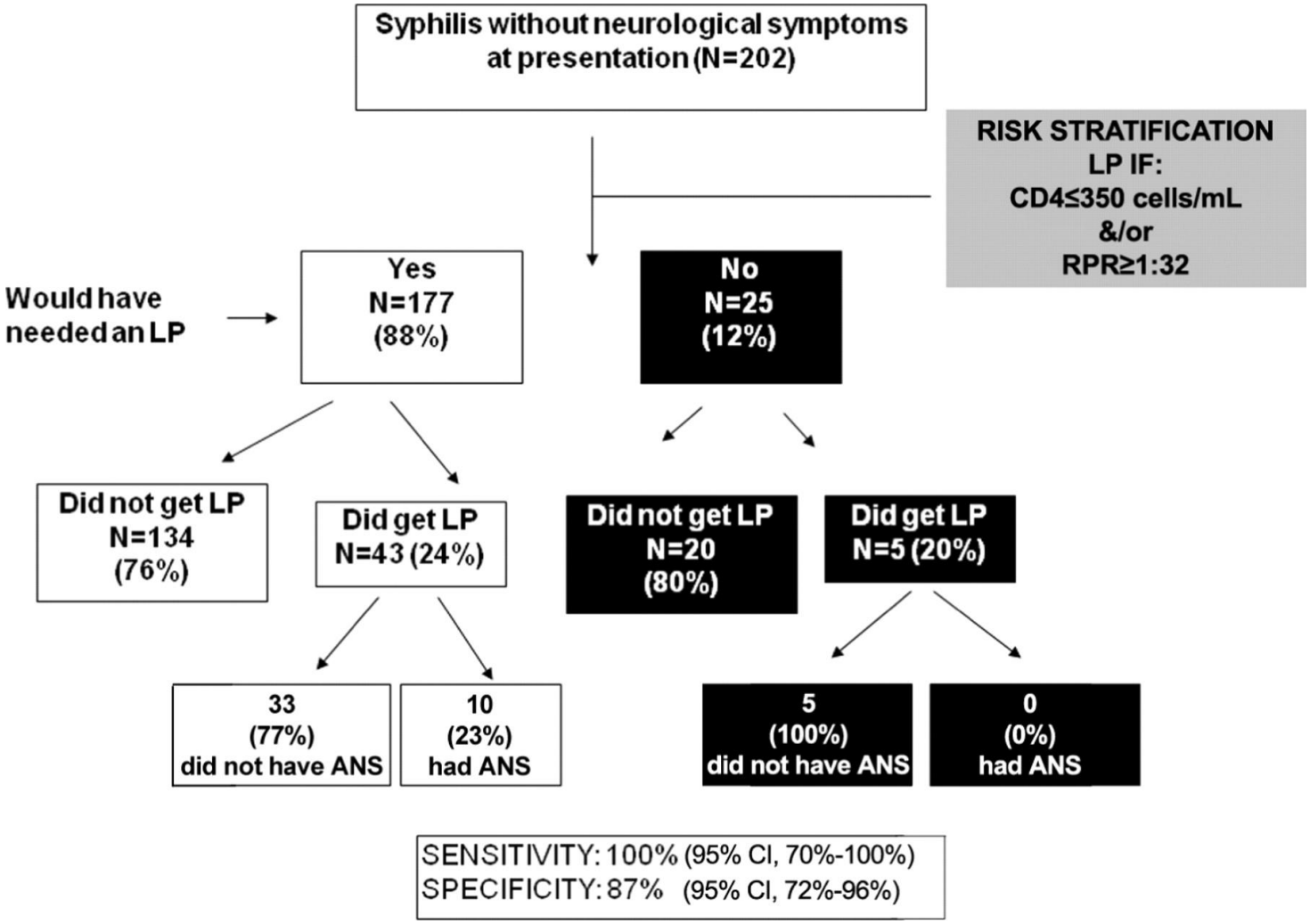


Diagnosis: Syphilis!

- RPR reactive @ 1:64
- FTA-Abs 2+ reactive

Would you do an LP now?

Retrospective application of the second risk stratification criterion, which was based on performance of a lumbar puncture (LP) in patients with a CD4 cell count <350 cells/mL and/or a rapid plasma reagin (RPR) titer ⩾1:32.



Khalil G. Ghanem et al. Clin Infect Dis. 2009;48:816-821

LP results

- CSF:
  - 29 WBCs (90% lymphs); 0 RBCs
  - Protein elevated at 108
  - Glucose normal at 51
  - Gram stain with 1+ WBCs, no organisms
  - VDRL reactive @ 1:2

Explanation

- Patient's partner had moved to New Mexico and they are now in a long-distance relationship
- While the patient is monogamous, the partner is not
- Last sexual activity in mid-late December
- Always uses condoms with sexual intercourse, but never uses condoms with oral sexual activity as did not consider this a high risk activity

Key Points

- Initial chancre was likely in his throat & thus not observed
  - The median incubation period for syphilis is 3 weeks
  - Regional LAD typically accompanies the primary lesion
- Syphilis can involve the hair follicles & was likely the cause of the patchy alopecia
- White, lichenified plaques on the palms were likely condyloma lata
- Initial negative RPR was a false negative either due to:
  - Humoral antibodies had not yet developed (20-30% of patients with primary syphilis have a negative RPR) OR
  - Prozone reaction: the presence of excess antibody interferes with the clumping of the Ag-Ab complex (occurs in < 2% of samples)
- Syphilitic hepatitis accounts for his disproportionately high alk phos level

Treatment of Syphilis

- *Primary, secondary, or early latent < 1 year*
  - **benzathine PCN G 2.4 million units IM x 1**
    - PCN allergic: doxycycline 100mg po bid x 14 days
    - if duration > 1 year or unknown
      - 3 doses @ 1 week intervals = 7.2 million units total
        - or doxycycline 100mg PO bid x 28 days
        - good reason to do at least yearly syphilis screening!!
- *Neurosyphilis*
  - **aqueous PCN G 18-24 million units IV QD x 14 days**
    - via continuous infusion best (otherwise dosed Q4)
    - PCN allergic: desensitize
    - optic or otic syphilis treated as neurosyphilis

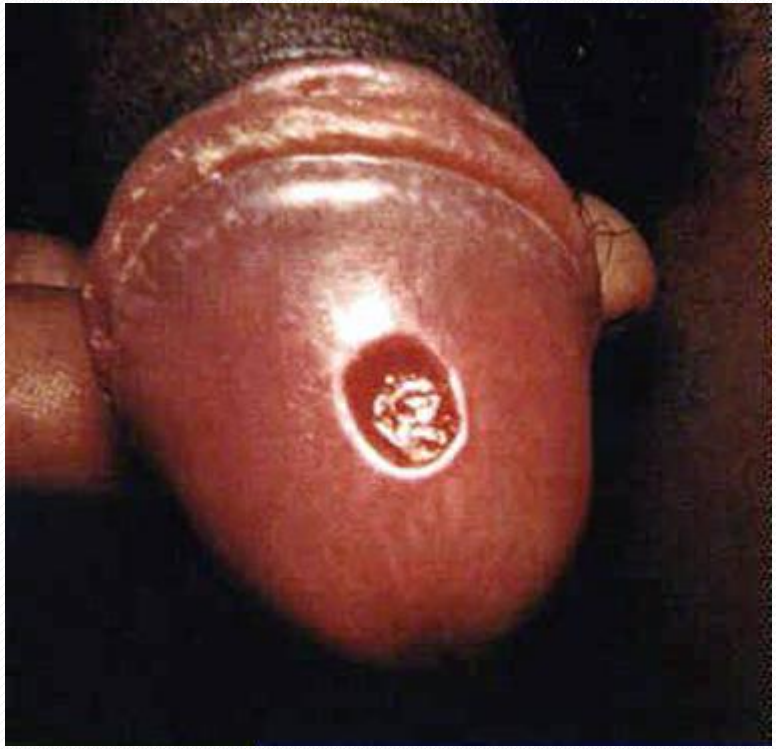
Follow-up

- Pt treated with a 14 day course of IV PCN G 18 million units/24 hours via continuous infusion
- Pt began to feel markedly improved after 48 hours of starting IV PCN
- At completion of PCN course, malaise, sore throat, and polyarthralgias had resolved. He was walking normally and his energy level had returned.

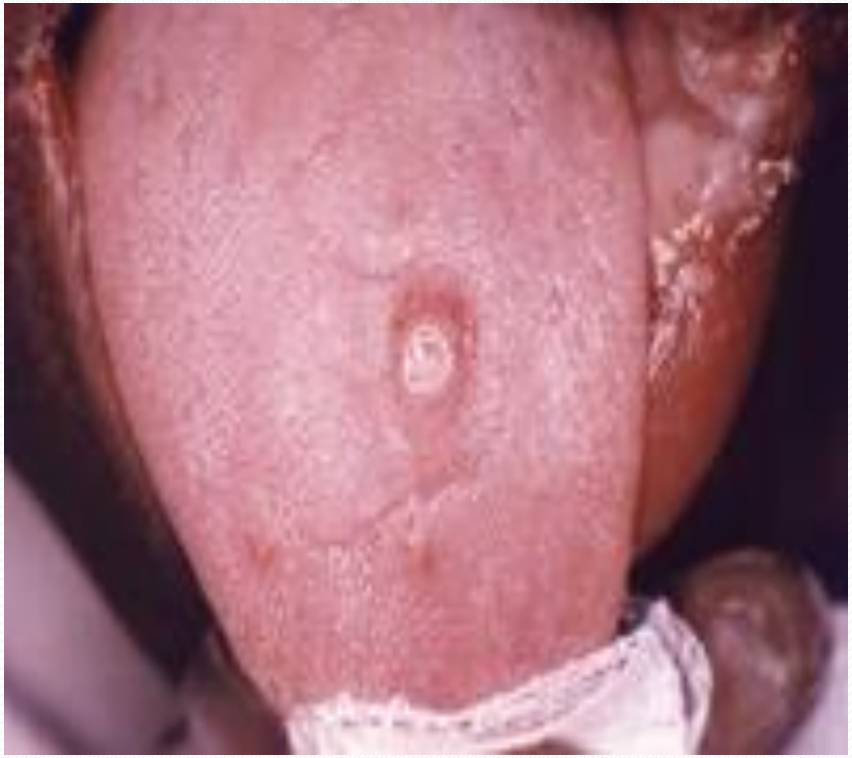
Darkfield micrograph of *Treponema pallidum*

Primary chancre

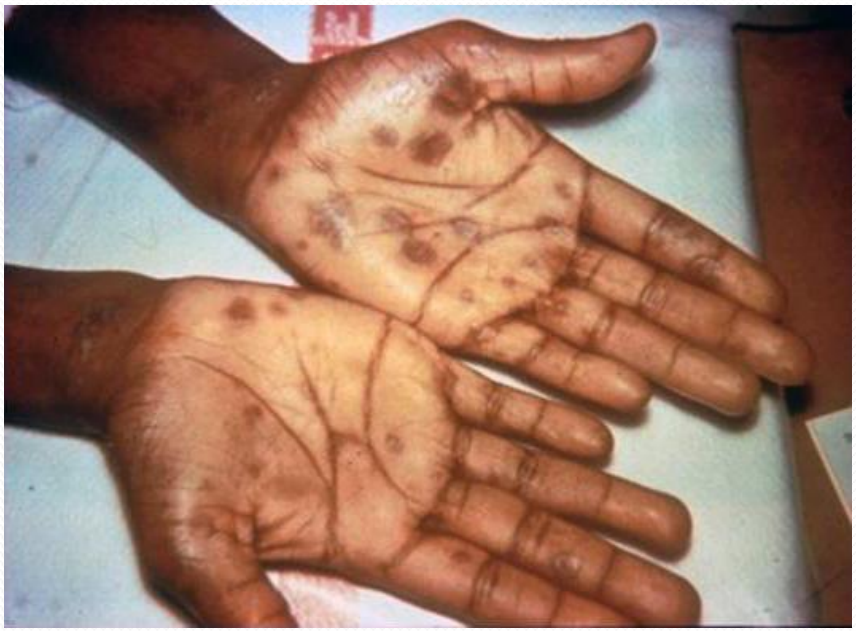
Genital

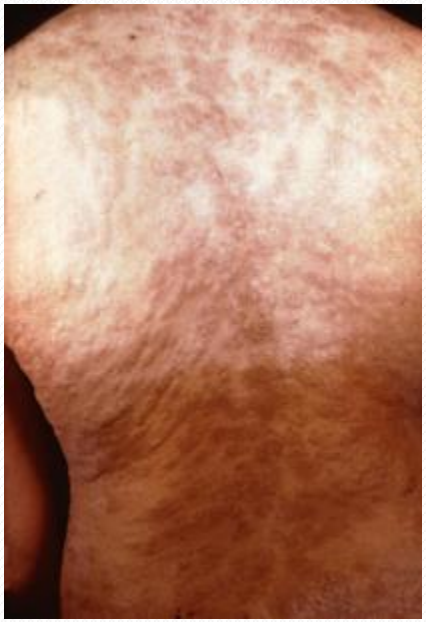


Oral



Secondary syphilis rash



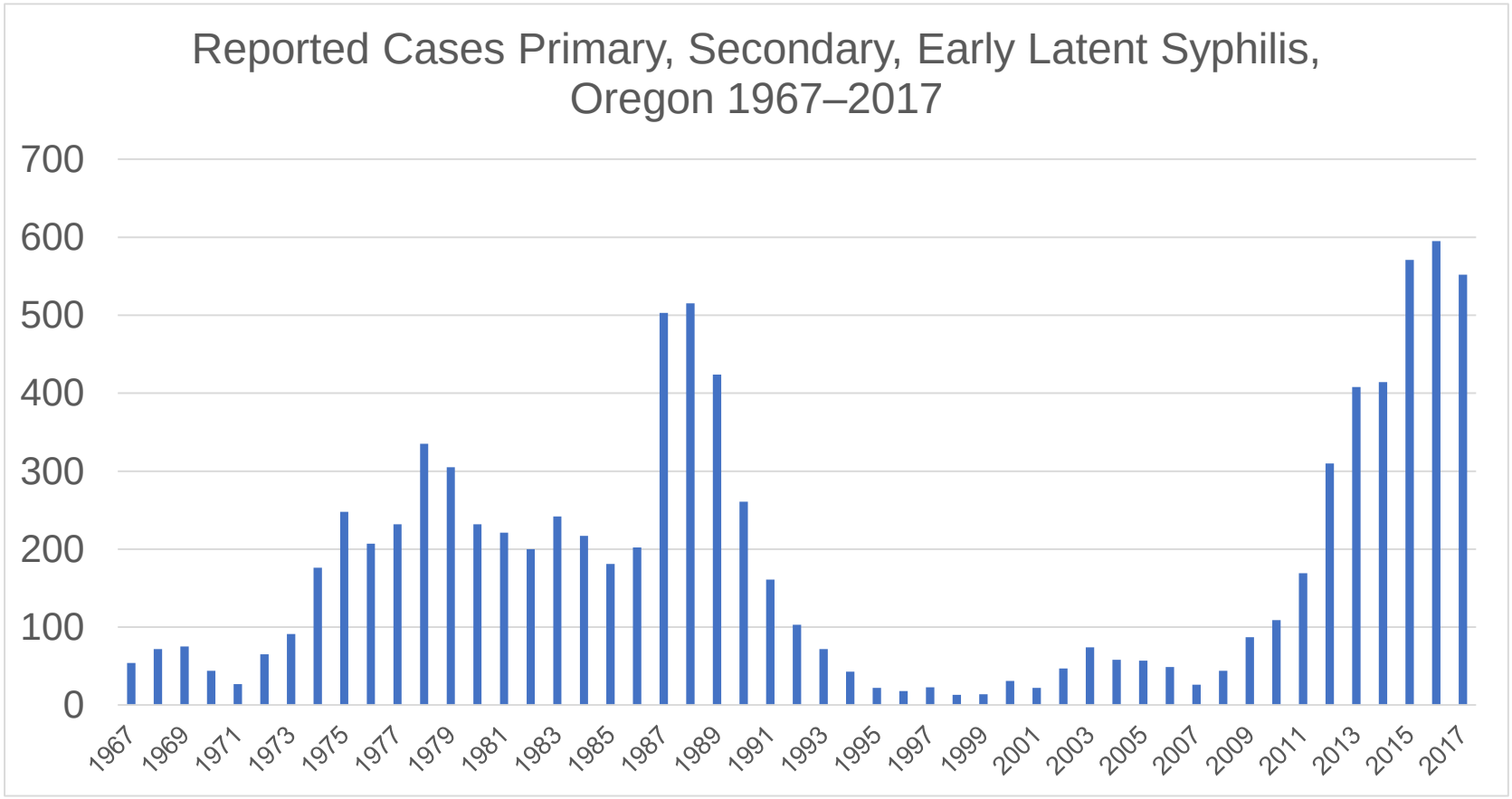


Syphilis causing migratory polyarthralgias?

- **Sexually transmitted arthritis syndromes.**
  - Medical Clinics of North America 1990 Nov;74(6):1617-31.
  - Keat, A.
- "Rheumatic syndromes, including arthralgia, inflammatory arthritis, and neuropathic arthritis, may occur during any stage of congenital or acquired syphilis."
- "Syphilitic synovitis responds well to antibiotic therapy"

Syphilis: It's Back!

1967 - 2017



Syphilis has achieved ***epidemic*** levels in Oregon, increasing over 2000% from 2007 to 2016.

FIGURE 1

Syphilis (primary, secondary, or early latent) by year, Oregon & U.S.

Source: Oregon Reportable Diseases Database and CDC (U.S. data)

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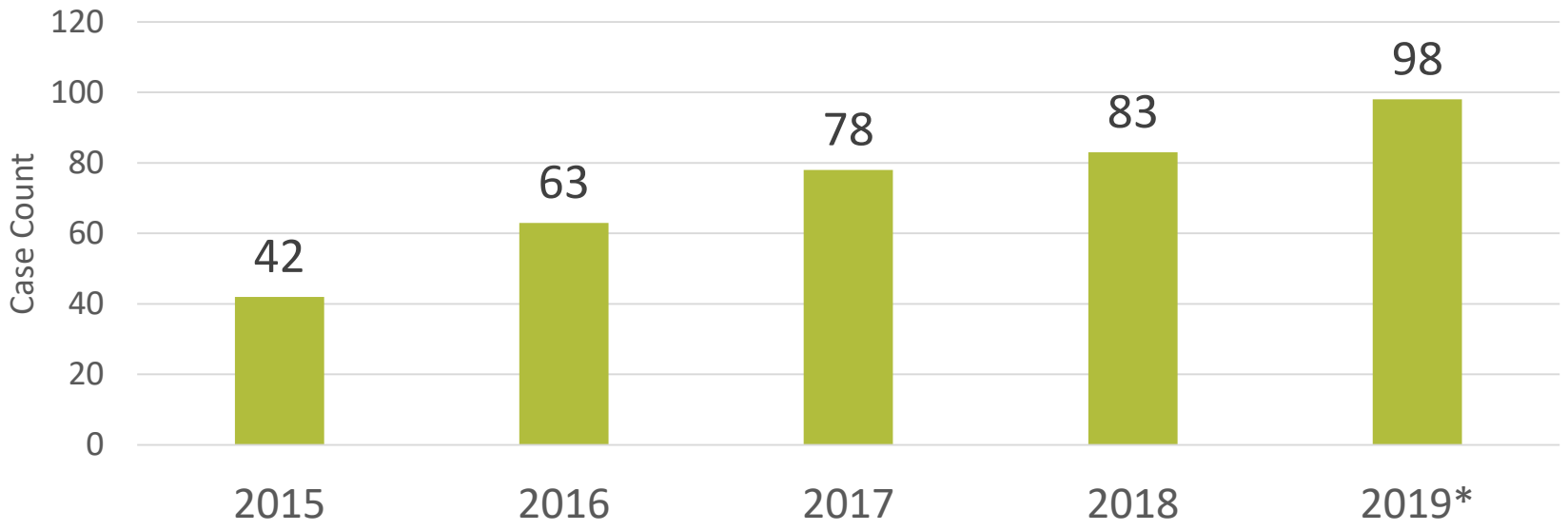
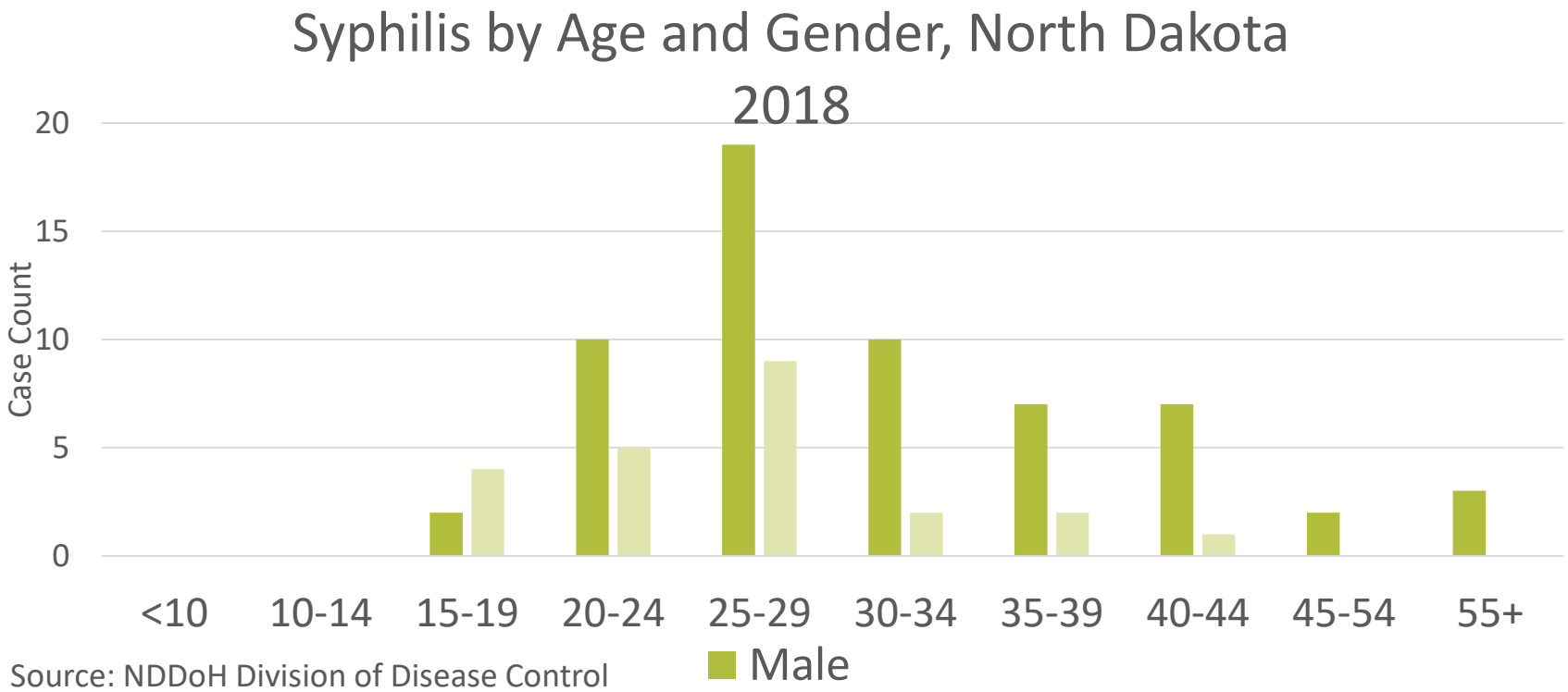
Syphilis (all stages), North Dakota 2015-2019*



Source: NDDoH Division of Disease Control

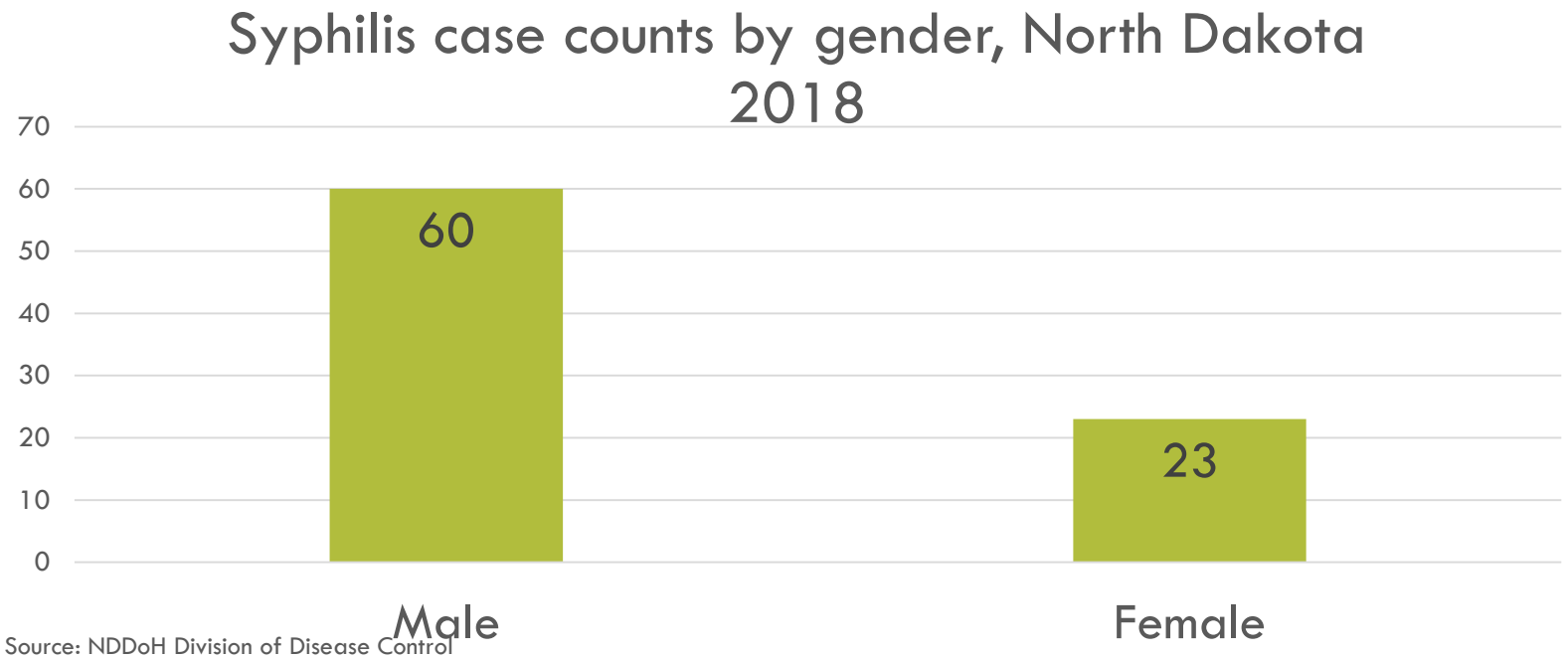
*Prelimina

66% of syphilis infections were in patients between 20 and 34 years of age in 2018



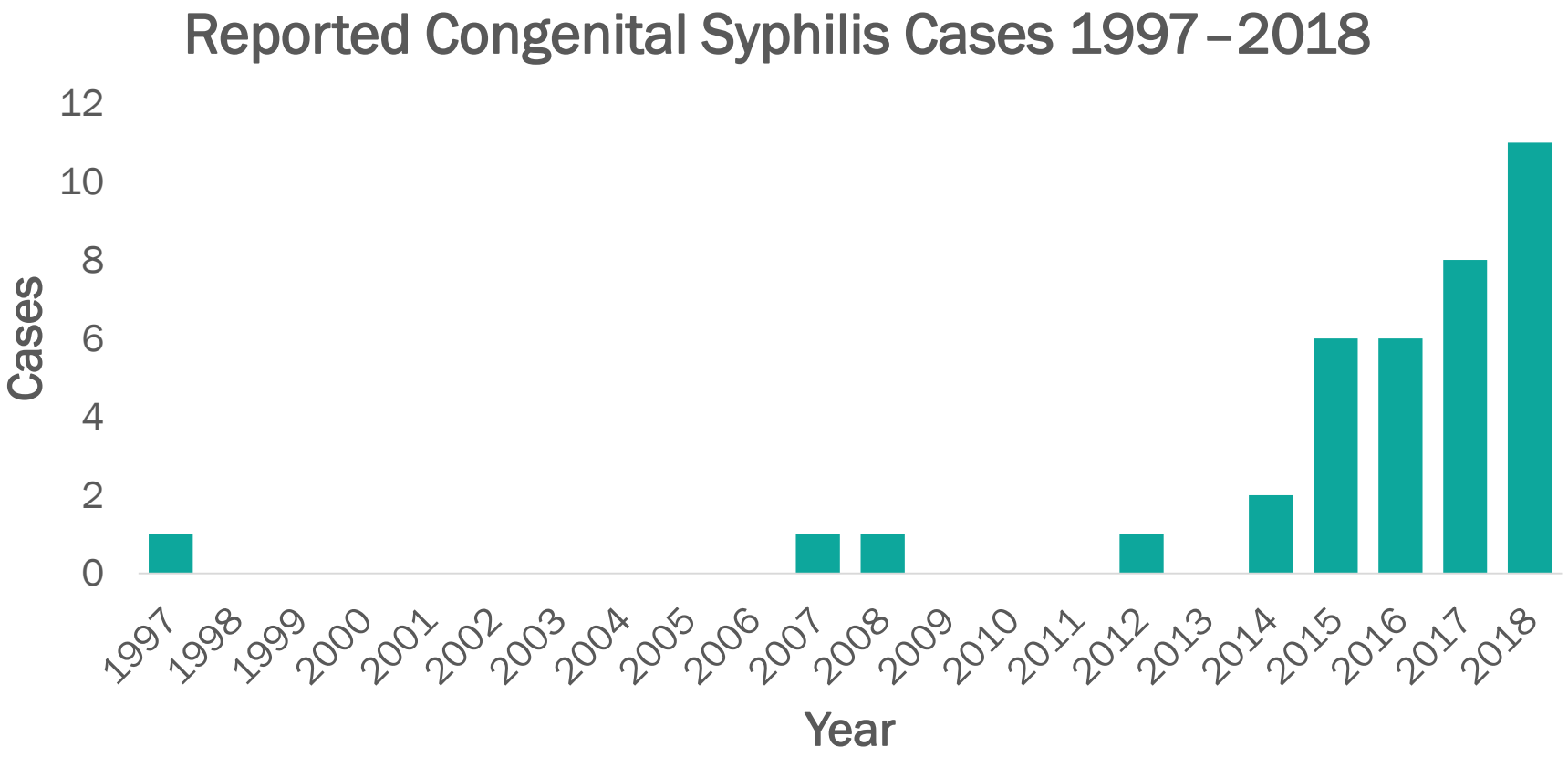
Source: NDDoH Division of Disease Control

60 syphilis infections in 2018 were in male patients and 53% of these patients reported having sex with other men



Source: NDDoH Division of Disease Control

Congenital Syphilis Cases in Oregon
1997 - 2018



Take-home points

- Think about syphilis – “the great mimicker” when sexually active patients present with an unusual constellation of symptoms
- Remember that the primary chancre of syphilis may be located in a place that you can’t see it, e.g. the oropharynx or rectum in MSM
- Every patient at high risk for STIs should have an RPR drawn Q 3-6 months
- Have a very low threshold to perform an LP in an HIV patient with syphilis, particularly if low CD4 count (< 350)or high RPR titer (≥ 1:32) and/or neurologic, otic or optic complaints

Summary: STIs

- Gonorrhea has become increasingly resistant to antibiotics, so now our first line treatment for gonorrhea is:
  - **IM ceftriaxone + PO azithromycin**
- If urethritis does not respond to standard therapy for Gonorrhea + Chlamydia, consider
  - drug-resistant GC (obtain specimen for culture & sensitivity testing)
  - Mycoplasma genitalium (send NAAT & trial of moxifloxacin)
- Treat suspected/confirmed syphilis with penicillin
  - route (IM vs IV) & duration are dependent upon stage/duration of infection
  - screen for syphilis frequently (e.g. Q 3months) in high-risk populations (e.g. MSM with multiple partners)

Routine screening

Syphilis serology

Pharyngeal GC/CT

Urine/Vaginal GC/CT

Rectal GC/CT

The primary chancre of syphilis is painless and if in the rectum, is not visible. So, if you can't see it and you can't feel it….

5-10 % of cases of gonococcal urethritis and up to 42% of NGU are asymptomatic

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HRSA Ryan White & Global HIV/AIDS Programs

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National STD Curriculum

www.std.uw.edu features self-study modules and Question Bank (board-review style) on a variety of STDs.

Hepatitis C Online

www.hepatitisc.uw.edu features self-study modules for diagnosis, monitoring, and management of HCV infection; tools and calculators; HCV medications; and a resource library.

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Questions? Discussion…

For clinical consultation and future training needs contact the Oregon AIDS Education and Training Center

www.oraetc.org

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